PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference C1-A0605P	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/JP2007/057036	International filing date *(day/month/year)* 30 March 2007 (30.03.2007)	Priority date *(day/month/year)* 31 March 2006 (31.03.2006)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant CHUGAI SEIYAKU KABUSHIKI KAISHA		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

- [x] Box No. I — Basis of the report
- [ ] Box No. II — Priority
- [ ] Box No. III — Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- [ ] Box No. IV — Lack of unity of invention
- [x] Box No. V — Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- [ ] Box No. VI — Certain documents cited
- [ ] Box No. VII — Certain defects in the international application
- [ ] Box No. VIII — Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 21 October 2008 (21.10.2008)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Yoshiko Kuwahara e-mail: pt07.pct@wipo.int

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

	Date of mailing *(day/month/year)*	
Applicant's or agent's file reference **C1-A0605P**	**FOR FURTHER ACTION** See paragraph 2 below	
International application No. **PCT/JP2007/057036**	International filing date *(day/month/year)* **30.03.2007**	Priority date *(day/month/year)* **31.03.2006**
International Patent Classification (IPC) or both national classification and IPC		
Applicant **CHUGAI SEIYAKU KABUSHIKI KAISHA**		

1. This opinion contains indications relating to the following items:

- ☒ Box No. I — Basis of the opinion
- ☐ Box No. II — Priority
- ☐ Box No. III — Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV — Lack of unity of invention
- ☒ Box No. V — Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI — Certain documents cited
- ☐ Box No. VII — Certain defects in the international application
- ☐ Box No. VIII — Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/JP	Date of completion of this opinion	Authorized officer
Facsimile No.		Telephone No.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/JP2007/057036

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ the translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rule 12.3(a) and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material

      ☒ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material

      ☐ on paper

      ☒ in electronic form

   c. time of filing/furnishing

      ☒ contained in the international application as filed

      ☐ filed together with the international application in electronic form

      ☐ furnished subsequently to this Authority for the purposes of search

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/JP2007/057036

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-28	YES
	Claims		NO
Inventive step (IS)	Claims		YES
	Claims	1-28	NO
Industrial applicability (IA)	Claims	1-28	YES
	Claims		NO

2. Citations and explanations:

Document 1: KHAWLI L. A. et al., Improved tumor localization and radioimaging with chemically modified monoclonal antibodies., Cancer Biothr. Radiopharm., 1996, Vol. 11, No. 3, pp. 203-215

Document 2: YAMASAKI Y. et al., Pharmacokinetic analysis of in vivo disposition of succinylated proteins targeted to liver nonparenchymal cells via scavenger receptors: importance of molecular size and negative charge density for in vivo recognition by receptors., J. Pharmacol. Exp. Ther., 2002, Vol. 301, No. 2, p. 467-477

Document 3: TEN KATE C. I. et al., Effect of isoelectric point on biodistribution and inflammation: imaging with indium-111-labelled IgG., Eur. J. Nucl. Med., 1990, Vol. 17, No. 6-8, p. 305-309(abstract) Database BIOSIS PREVIEWS[online], [retrieved on 13 April 2007] Retrieved from: Dialog Information Services, Biosis no. 199191074220.

Document 4: DEL RIO G. et al., Effect of An engineered penicillin acylase with altered surface charge is more stable in alkaline pH., Ann. NY Acad. Sci., 1996, Vol. 799, p. 61-64

Document 5: ONDA M. et al., Lowering the Isoelectric Point of

the Fv Portion of Recombinant Immunotoxins Leads to Decreased Nonspecific Animal Toxicity without Affecting Antitumor Activity., Cancer Res., 2001, Vol. 61, No. 13, p. 5070-5077

Document 6: WO 1998/03546 A1 (AMGEN Inc.), 29 January 1998, claim 1

The inventions of claims 1-28 do not involve an inventive step in view of documents 1-6 cited in the ISR.

Although an antibody is a positively charged protein and a mammalian cell is negatively charged, the efficiency of the antigen-antibody interaction may be decreased by a nonspecific interaction between those oppositely charged molecules; therefore, document 1 discloses that a monoclonal antibody was chemically modified to lower the isoelectric point of the antibody, which in turn decreased the nonspecific interaction between the antibody and the cell, thereby decreasing the transfection of the antibody into a normal organ, i.e., causing a change in blood kinetics (abstract, and page 204, left column, lines 20-36).

Document 2 discloses that IgG, which has a lower isoelectric point due to succinylation, is transfected into hepatic nonparenchymal cells.

Document 3 discloses that IgG's having different isoelectric points were produced by changing the level of DTPA, and further that 0.9 and 3.7 DTPA/IgG showed faster clearance from the circulation.

Document 4 discloses a penicillin acylase in which a site-specific variation of the polypeptide portion of a surface protrusion is induced from the conformation based on

the amino acid sequence so as to produce a variant where the number of positively charged amino acid residues is increased.

Document 5 discloses an immunotoxin in which pseudomonas exotoxin is fused to an Fv fragment of an antibody, wherein the isoelectric point is lowered by replacing the neutral amino acid in a framework region of the Fv fragment, which is a variable region, with an acidic amino acid.

Document 6 discloses that an amino acid residue is substituted in a protein to lower the isoelectric point.

In the inventions described in documents 1-3, a person skilled in the art could easily conceive of employing a method to substitute the amino acid residues being exposed out of the surface of a protein by positively charged amino acid residues, as described in documents 4-6, as the means for lowering the isoelectric point of the antibody.

Moreover, the conformation of antibodies has already been analyzed, and the positions of amino acid residues exposed out of the surface are also known; therefore, a person skilled in the art could easily conceive of selecting the positions prescribed in claim 23 as the positions for amino acid substitution.